REMARKS

Claims 1, 2, 4-23 and 25 are pending in the present application. Claims 1, 9 and 25 have been amended. Claims 1 and 25 have been amended by canceling the prophylaxis method, and claim 1 has also been amended by deleting certain diseases and disorders which are to be treated. Claim 9 has been amended to correct a grammatical error. No new matter has been added by way of the above amendments.

Issues under 35 U.S.C. § 112

Claims 1-9, 24 and 25 have been under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the specification does not enable the prophylaxis of the claimed diseases and further lacks enablement for the treatment of some of the diseases recited.

Applicants have canceled the phrase "prophylaxis and/or" from independent claim 1. Therefore, the rejection as to this aspect of the claims has been overcome.

Regarding the rejection of the treatment of certain diseases, the Examiner has found enabling support for chronic heart failure, angina, cardiac infarction, cerebral infarction, pollakiuria, urinary incontinence and cerebral ischemia. Of the remaining diseases, Applicants have now deleted from the claims the following diseases: premature birth, subarachnoid hemorrhage, cerebral apoplexy, peripheral blood vessel disorder, anxiety, male pattern baldness, other diabetic complication, sterility, urolithiasis and pain accompanied thereby, nocturnal enuresis, asthma, chronic obstructive pulmonary disease (COPD), and cough accompanied by asthma or chronic obstructive pulmonary disease (COPD). This leaves 7 diseases which allegedly lack enabling support but have not been deleted from the claims. These diseases are: hypertension, irritable bowel syndrome, cerebral infarction, cerebral vasospasm, cerebral hypoxia, traumatic encephalopathy and erectile dysfunction. Applicants disagree that these diseases lack enabling support for the following reasons.

The compounds of the present invention possess a large conductance calcium-activated K channel (also referred to as a BK channel) opening activity. This has been demonstrated in Experimental Examples 1 and 2 on pages 67-70 of the specification. By these experiments, the Applicants were able to confirm that the relaxation effects on potassium-induced bladder contractions and the inhibitory effects on P-substance-induced bladder contractions of the presently claimed compounds were blocked and reduced by iberiotoxin, which is a selective large conductance calcium-activated K channel blocker (see page 70, lines 6-16). From this, it was discovered that the claimed compounds compete with a selective BK channel blocker, iberiotoxin. Based on this finding, the claimed compounds were confirmed to have BK channel opening activity, and Applicants assert that the skilled artisan would recognize this activity as well. It follows, then, that the skilled artisan would also understand that the claimed compounds could be useful in treating the claimed diseases.

Furthermore, the Applicants submit herewith evidence in the form of 11 references which demonstrates that BK Channel openers are capable of treating the claimed diseases. As will be seen from the discussion that follows, one of ordinary skill in the art would immediately recognize that the claimed compounds could be used to treat the diseases at issue in this rejection (the 7 diseases listed above). These supporting references are:

Exhibit 12, Nature 407, 870-876, 2000

Exhibit 13, Circulation Res. 87, e53-e60, 2000

Exhibit 14, N. Engl. J. Med. 344, 1846-1850, 2001

Exhibit 15, Am. J. Physiol. 268, C619-C627, 1995

Exhibit 16, Am. J. Physiol. 277, G22-G30, 1999

Exhibit 17, Nature Med. 7, 471-477, 2001

Exhibit 18, Neurological Research 21, 705-711, 1999

Exhibit 19, Stroke 33, 802-808, 2002 (Mar)

Exhibit 20, J. Clin. Invest. 104, 577-588, 1999

Exhibit 21, Neurosci. Lett. 332, 163-166, 2002 (8 Nov)

Exhibit 22, Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H600-H608, 1998

Hypertension

The Examiner noted at the bottom of page 2 of the Office Action of June 10, 2008 that Exhibit 4 (Current Pharmaceutical Design, Vol. 2, No. 4, 1996, pp. 413-428) which discusses hypertension "further states that 'another study reported that intravenous administration of NS 004 reduced mean arterial blood pressure but no effect on blood pressure was observed. It was concluded that the cardiovascular effects of NS 004 could be ascribed to the blockade of calcium channels, rather than the opening of BK channels.'" This excerpt was cited as an example to support the Examiner's assertion that the references did not provide definitive support that BK channels could be used to treat all of the diseases claimed (in this instance, hypertension). However, the excerpt relied upon by the Examiner merely indicates that the action mechanism of NS 004 is the blockade of calcium channels. This does not demonstrate that BK channel openers are not effective in treating hypertension.

Irritable bowel syndrome

The Examiner states that the treatment of irritable bowel syndrome (IBS) is determined by the patient's symptoms, and that the specification does not reasonably provide enablement for a method of treating IBS. In response, Applicants submit **Exhibit 15** which demonstrates that BK channels are important regulators of colonic motility and are effective in treating bowel movements (diarrhea or constipation) and bowel motility.

Exhibit 16 further supports this position by demonstrating that the BK channel is the predominant channel type in colon epithelium. The water and salt homeostasis of the organism is partly maintained by regulated absorption and secretion of NaCl across specialized epithelial cells in the distal colon. It is therefore expected that BK channels can be used to treat bowel movements (diarrhea or constipation) and changes in the form of the stool (loose, watery, or pellet-like).

Additionally, **Exhibit 10** (submitted previously) shows that BK channels are in the intestinal intrinsic primary afferent neurons. BK channels reduce the firing of the neurons to relax visceral hypersensitivity. It is therefore expected that BK channels can be used to treat visceral hypersensitivity.

Based on the above evidence, Applicants assert that one of ordinary skill in the art would immediately recognize that the claimed compounds, which have BK channel opening activity, could be used to treat IBS.

Remaining claimed diseases

With regard to the remaining clamed diseases (cerebral infarction, cerebral vasospasm, cerebral hypoxia, traumatic encephalopathy and erectile dysfunction), and in further support of the arguments for the enablement of hypertension and IBS, Applicants refer the Examiner to the supporting references and specific excerpts found therein which are summarized here.

Specific citations :

Hypertension	**Nature 407, 870-876, 2000** "Here we show that targeted deletion of the gene for the β1 subunit leads to a decrease in the calcium sensitivity of BK channels, a reduction in functional coupling of calcium sparks to BK channel activation, and increases in arterial tone and blood pressure." (p.870, abstract L.5) "The knockout mice exhibited an increase in mean blood pressure, even over the pure 129svj mice (Fig. 7a). These data indicate that the increased arterial tone leads to an elevation in blood pressure." (p.873, right col. L.25) "Figure 7 β1-KO mice show symptoms of hypertension. a, Mean blood pressure of β1-KO and control 129svj mice. Control average blood pressure is 114±6.0 mm Hg (n=6), KO average blood pressure is 134±5.1mmHg (n=6), P=0.029." (p.875, Figure 7) **Circulation Res 87, e53-e60, 2000** "The effects of disrupting the BKβ1 subunit on blood pressure regulation were investigated in conscious, unrestrained mice with chronically implanted catheters. Baseline values of heart rate and blood pressure were recorded in each mouse twice over 1 hour on two separate days. While heart rates were similar in both groups of mice (608 ± 14 bpm in BKβ1 +/+, n=9; 642 ± 15 bpm in BKβ1-/-, n=58), blood pressure was significantly elevated in BKβ1 -/- mice in comparison to BKβ1 +/+ mice (116 ± 2 versus 103 ± 1 mm Hg; P=0.001)." (p.6, left col. L.36)
irritable bowel syndrome	**N Engl J Med 344, 1846-1850, 2001** "The irritable bowel syndrome is defined on the basis of the recently modified Rome criteria as the presence for at least 12 weeks (not necessarily consecutive) in the preceding 12 months of abdominal discomfort or pain that cannot be explained by structural or biochemical abnormalities and that has at least two of the following three features: pain is relieved with defecation, its onset is associated with a change in the frequency of bowel movements (diarrhea or constipation), or its onset is associated with a change in the form of the stool (loose, watery, or pellet-like)." (p.1846, left col. L.12) "Altered bowel motility, visceral hypersensitivity, psychosocial factors, an imbalance in neurotransmitters, and infection have all been proposed as playing a part in the development of the irritable bowel syndrome (Fig. 1)." (p.1846, right col. L.13) **Am J Physiol 268, C619-C627, 1995** "The role of Ca^{2+}-activated K^+ channels (BK channels) in the canine colon was evaluated by testing the effects of charybdotoxin (ChTX) and tetraethylammonium on K^+ currents of isolated myocytes and on electrical and mechanical activity of tissue strips. ChTX blocked Ca^{2+}-activated outward current [$I_{K(Ca)}$] in a dose- and voltage-dependent manner. No significant differences in $I_{K(Ca)}$ density, ChTX block, or Ca^{2+} sensitivity of BK channels were observed between circular and longitudinal myocytes. ChTX (100 nM) blocked 60% of current at +80 mV. Delayed rectifier current was not inhibited by 100 nM ChTX. In the absence of agonists, ChTX did not affect electrical or mechanical activity of circular muscle strips. In the presence of 10^{-6} M BAY K 8644 or 10^{-5} M acetylcholine, ChTX increased slow-wave duration and amplitude, induced membrane potential oscillations, and potentiated contraction. In unstimulated longitudinal muscle strips, ChTX depolarized the tissue, increased burst duration and spiking frequency, and resulted in an increase in contractions. These results indicate that BK channels are important regulators of colonic motility." (p.C619, abstract) **Am J Physiol 277, G22-G30, 1999** "The Ca^{2+}-activated maxi K^+ channel is an abundant channel type in the distal colon epithelium, but nothing is known regarding the actual number and precise localization of these channels. The aim of this study has therefore been to quantify

	the maxi K^+ channels in colon epithelium by binding of iberiotoxin (IbTX), a selective peptidyl ligand for maxi K^+ channels. In isotope flux measurements 75% of the total K^+ channel activity in plasma membranes from distal colon epithelium is inhibited by IbTX ($K_{0.5}$=4.5 pM), indicating that the maxi K^+ channel is the predominant channel type in this epithelium." (p.G22, abstract (in part)) "The water and salt homeostasis of the organism is partly maintained by regulated absorption and secretion of NaCl across specialized epithelial cells in the distal colon (for reviews, see Refs. 6 and 16)." (p.G22, left col. L.1) **J Physiol 526, 375-385, 2000 (previously submitted on March 6, 2008: including additional specific citations)** (Abstract (full)) and "The sensory neurons within the gut wall are subjected to mechanical deformation of their processes and of their cell bodies. Deformation of the processes by stretch that occurs when the intestine is distended or the muscle contracts excites the neurons and triggers reflexes. Compression of the soma by pressure causes increased opening of potassium channels and thus has an inhibitory effect, which may be protective"(conclusion) "The IPANs form connections with each other, via slow excitatory synaptic connections, and they are extremely frequent, about 600 per millimetre length of gut (Kunze & Furness, 1999). Their neurites are excited by contraction of the gut, which pulls on connections with the neurons (Kunze et al. 1999). Thus, when the gut contracts, the neurons will be excited via their neurites and via synaptic inputs, but stretch of the soma membrane will be diminished, and inhibition via soma BK channels will be minimized. On the other hand, if the gut is distended and the muscle contracts against the distending force, inhibition via soma BK channels will be greater. It is possible that the stretch sensitivity of the soma channels plays a protective role, reducing the firing of the neurons and the intensity of reflexes, when the intestine contracts against a blockage that it fails (at least initially) to dislodge." (p.384, left col. L.17) (IPANs: intrinsic primary afferent neurons)
cerebral infarction	**US patent 6,184,231 B1, 2001 (previously submitted on March 6, 2008: including additional specific citations)** "All compounds were tested in at least 5 oocytes and are reported at the single concentration of 20uM; the effect of the selected compounds of Formula 1 on BK current was expressed as the percent of control IBTX-sensitive current and is listed in Table 1." (column 22, L.63) "Selected compounds have been evaluated in the focal stroke model involving permanent MCAO in the spontaneously hypertensive rat. This procedure results in a reliably large neocortical infarct volume that is measured by means of vital dye exclusion in serial slices through the brain 24 hours after MCAO. In the present test, compounds were administered using an intravenous route of administration at 2 hours after occlusion. For example, in this model, the compound of Example 21 reduced the cortical infarct volume by about 25% when administered (0.003 mg/kg) as a single bolus 2 hours after middle cerebral artery occlusion as compared to vehicle-treated (2% DMSO, 98% propylene glycol) control." (column 23, L.34) (MCAO : middle cerebral artery occlusion) **Nature Med 7, 471-477, 2001** "During ischemic stroke, neurons at risk are exposed to pathologically high levels of intracellular calcium (Ca^{++}), initiating a fatal biochemical cascade. To protect these neurons, we have developed openers of large-conductance, Ca^{++}-activated (maxi-K or BK) potassium channels, thereby augmenting an endogenous mechanism for regulating Ca^{++} entry and membrane potential. The novel fluoro-oxindoles BMS-204352 and racemic compound 1 are potent, effective and uniquely Ca^{++}-sensitive openers of maxi-K channels. In rat models of permanent large-vessel stroke, BMS-204352 provided significant levels of cortical

	neuroprotection when administered two hours after the onset of occlusion, but had no effects on blood pressure or cerebral blood flow. This novel approach may restrict Ca^{++} entry in neurons at risk while having minimal side effects." (p.471, abstract (full)) "The effects of the maxi-K channel openers were examined in two models of acute focal stroke. In each model, compound 1 or BMS-204352 was administered intravenously at two hours after permanent occlusion of the middle cerebral artery (MCA), with one exception: when the relative effect of drug at one or two hours after occlusion was compared (longer separations between occlusion onset and drug delivery were not explored). We conducted initial characterization of neuroprotective effects with compound 1. The time course of cortical infarct evolution over 24 hours following MCA occlusion was studied using magnetic resonance imaging (MRI) techniques in spontaneously hypertensive rats (SHR). Rats were administered compound 1 (0.3 mg/kg, i.v.) or vehicle at two hours after permanent MCA occlusion (Fig. 5a). We observed a significant reduction in cortical infarct volume in the compound-1–treated group at 5.5 and 24 hours after occlusion. In subsequent experiments using this model, BMS-204352 produced significant reductions in cortical infarct volume when tested at doses between 0.01 and 0.3 mg/kg." (p.474, left col. L.13) "Using a Wistar normotensive rat model incorporating permanent unilateral MCA occlusion, permanent ipsilateral common carotid artery (CCA) occlusion and transient (1 h) contralateral CCA occlusion, BMS-204352 and compound 1 at 1 mg/kg produced similar levels of neuroprotection (Fig. 5b). BMS-204352 produced significant reductions in cortical infarct volume when administered at doses between 1 μg/kg and 1 mg/kg (Fig. 5c), but was ineffective at 3 mg/kg. Other experiments demonstrated a minimal effective dose of 0.01 μg/kg, indicating an 'inverted-U' dose-response relationship similar to that observed in evoked potential experiments (see Fig. 3c). Reductions in infarct volume were typically 20–30%. BMS-204352 was equally effective when administered at one or two hours following occlusion (Fig. 5d, 0.3 mg/kg). These results demonstrate that maxi-K channel openers reduced cortical infarct volume following permanent MCA occlusion when administered at two hours following occlusion onset." (p.474, left col. L.35)
cerebral vasospasm	**Neurological Research 21, 705-711, 1999** "K^+ channel openers may be useful in the treatment of cerebral vasospasm following subarachnoid hemorrhage. However, the role of Ca^{2+}-dependent K^+ channel (K_{Ca}) openers in cerebral vasospasm remain unclear. This study was undertaken to examine the role of K_{Ca} in hemolysate-induced contraction of rabbit cerebral and peripheral arteries: 1. Iberiotoxin (IBTX), a selective K_{Ca} channel blocker, produced more pronounced contraction in basilar than in those of carotid or femoral arteries, indicating K_{Ca} channels are important regulating factors in cerebral arteries; 2. NS1619, a selective K_{Ca} channel opener, abolished the contraction of basilar artery to erythrocyte lysate, a causative agent for cerebral vasospasm; 3. In rabbit basilar artery, NS1619 relaxed the contractions to IBTX, erythrocyte lysate and KCl (20 and 60 mM), indicating that NS1619, besides opening K_{Ca} channels, possesses other vasodilating actions. We conclude that K_{Ca} channels are important factors in the regulation of cerebral vascular tension and K_{Ca} channel opener NS1619 may have dual relaxant actions in cerebral arteries. (p. 705, abstract (full)) **Nature 407, 870-876, 2000** "Cerebral arteries that lack the β1 subunit are significantly more constricted at a given pressure than are control arteries (Fig. 6a-c). These results indicate that the lack of the β1 subunit leads to an elevation in arterial tone. The contribution of theβ1 subunit to the regulation of arterial tone can be evaluated by examining the effects of the BK inhibitor iberiotoxin (IBTX) on arterial diameter. IBTX caused a

	74% increase in arterial tone in the control (Fig. 6d, f). In contrast, IBTX did not affect knockout cerebral arteries (Fig. 6e, f). These results indicate that BK channels lacking the β1 subunit are unable to contribute to the regulation of arterial tone." (p.873, right col. L.3) **Stroke 33, 802-808, 2002 (Mar)** "Increasing the extracellular K^+ concentration from 6 to 25 mmol/L contracted human cerebral artery segments to 52.4 ± 9.5% of their maximum level of force development, and the subsequent addition of iberiotoxin (100 nmol/L; a selective inhibitor of BK channels[8,21]) caused a further contraction to 80.3 ± 6.4% of tissue maximum ($P<0.05$ versus 25 mmol/L K^+; n=6) (Figure 5A and 5B)." (p.805, left lower) "We propose that in the human cerebral vasculature, Ca^{2+} sparks via the activation of plasmalemmal BK channels promote membrane hyperpolarization and cerebral artery relaxation (Figure 6)." (p.806, left lower) "In conclusion, we provide the first demonstration of Ca^{2+} sparks and their associated BK channel currents in human cerebral artery myocytes. Furthermore, we provide support that this pathway plays a role in the regulation of human cerebral artery contraction." (p.807, right col. L.21)
cerebral hypoxia	**J Clin Invest 104, 577-588, 1999** "A low-O_2 medium (PO_2 = 10–20 mmHg) markedly inhibited this BK_{Ca} channel open probability in a voltage-dependent manner in cell-attached patches, but not in insideout patches, indicating that the effect of O_2 deprivation on BK_{Ca} channels of mice neocortical neurons was mediated via cytosol-dependent processes." (p.577, abstract L.8) "Because of their large conductance and prevalence in the neocortex, BK_{Ca} channels may be considered as a target for pharmacological intervention in conditions of acute anoxia or ischemia." (p.577, abstract L.18) **Neurosci Lett 332, 163-166, 2002 (8 Nov)** "To determine the role of Ca^{2+}-activated K^+ channels in hyperexcitability, we measured large unitary conductance (>200 pS, BK_{Ca}) currents in symmetrical 140/140 mM K^+ using inside-out configuration in CA1 pyramidal cells acutely dissociated from the hippocampus of rats exposed to normoxia or hypoxia (at 10% inspired O_2) for 4 weeks after birth. About 53% of the patches contained BK_{Ca} channels in the normoxic group, but only 20% in the hypoxic one. There were no differences in channel conductance or reversal potential between the groups. Yet, the open probability of BK_{Ca} channels was much less in hypoxic neurons than that in the control, because of a decrease in channel open time and a prolongation of the closed time." (p.163, abstract L.2) "In support of our hypothesis, neurons in the hypoxic group had less BK_{Ca} channel activity than the normoxic controls, suggesting that Ca^{2+}-activated K^+ channels can be modulated by hypoxia and that the reduction in BK_{Ca} channel activity can play a role in the hypoxia-induced neuronal hyperexcitability. Our results are consistent with previous findings showing that the BK_{Ca} channel is a target for modulation in hypoxia." (p.165, right col. L.16)
traumatic encephalopathy	**J Cereb Blood Flow Metab 21, 396-403, 2001 (previously submitted on March 6, 2008: including additional specific citations)** "The authors evaluated the effects of postinjury systemic administration of the maxi-K channel opener, BMS-204352, on behavioral and histologic outcome after lateral fluid percussion (FP) traumatic brain injury (TBI) in the rat. Anesthetized Sprague-Dawley rats (n=142) were subjected to moderate FP brain injury (n=88) or surgery without injury (n=54) and were randomized to receive a bolus of 0.1 mg/kg BMS-204352 (n=26, injured; n=18, sham), 0.03 mg/kg BMS-204352 (n=25, injured; n=18, sham), or 2% dimethyl sulfoxide (DMSO) in polyethylene glycol (vehicle, n=27, injured; n=18, sham) at 10 minutes postinjury. One group

	of rats was tested for memory retention (Morris water maze) at 42 hours postinjury, then killed for evaluation of regional cerebral edema. A second group of injured/sham rats was assessed for neurologic motor function from 48 hours to 2 weeks postinjury and cortical lesion area. Administration of 0.1 mg/kg BMS-204352 improved neurologic motor function at 1 and 2 weeks postinjury ($P<0.05$) and reduced the extent of cerebral edema in the ipsilateral hippocampus, thalamus, and adjacent cortex ($P<0.05$). Administration of 0.03 mg/kg BMS-204352 significantly reduced cerebral edema in the ipsilateral thalamus ($P<0.05$). No effects on cognitive function or cortical tissue loss were observed with either dose. These results suggest that the novel maxi-K channel opener BMS-204352 may be selectively beneficial in the treatment of experimental TBI." (p.396, abstract left col. L.5) "Acute, postinjury administration of the maxi-K channel opener BMS-204352 significantly attenuated regional cerebral edema formation at 48 hours and markedly improved neurologic motor function at 1 and 2 weeks after lateral FP brain injury in rats." (p.399, right col. L.55) "These beneficial results, in a clinically relevant model of brain injury, are suggestive of the potential use of this maxi-K channel opener as a therapeutic agent for the treatment of TBI, and future studies should attempt to assess the therapeutic window for this compound." (p.401, right col. L.1)
erectile dysfunction	**US patent 6,184,231 B1, 2001 (previously submitted on March 6, 2008: including additional specific citations)** "All compounds were tested in at least 5 oocytes and are reported at the single concentration of 20uM; the effect of the selected compounds of Formula 1 on BK current was expressed as the percent of control IBTX-sensitive current and is listed in Table 1." (colum 22, L.63) "The in vivo model on erectile function is described fully in the scientific literature [Rehman, J., Chenven, E., Brink, P. Peterson, B., Wolcott, B., Wen, Y. P., Melman, A., Christ, G.: Diminished neurogenic but not pharmacological erections in the 2- to 3-month experimentally diabetic F-344 rat. Am. J. Physiol. 272: H1960-H1971, (1997)]. Briefly, rats (250-600 g) were anesthetized using sodium pentobarbital, the abdomen opened and the cavernous nerve identified. A pressure catheter was placed in the right corpus cavernosum (crus) to measure intracavernous pressure (ICP). A second catheter was introduced into the carotid artery to measure blood pressure. Test compound (0.1, 0.3 and 1 mg/kg iV.) or vehicle (PEG 400) was given via a catheter placed into the jugular vein. Control intracavernous pressure responses were elicited by electrically stimulating the cavernous nerve via bipolar stimulating electrodes (20 Hz, 0.22 ms pulse width). Stimulus amplitude (0.2-20 mA) was adjusted to produce a submaximal intracavernous pressure response (typically 0.2 or 0.5 mA). A series of control intracavernous pressure responses were then obtained using a constant stimulus amplitude. Test compound or vehicle was then administered (200 .mu.l i.v bolus) and the cavernous nerve was restimulated to evoke a cavernous pressure response at various times post-drug administration. Animals were excluded from the study if the initial ICP responses to nerve stimulation were unstable ("spiky" responses) or if there were time-dependent variations in the magnitude of the control responses. Animals were also excluded if the control ICP/BP response fell outside the 0.3-0.6 range. A repeated measures ANOVA was used for the evaluation of statistical significance. The compound of Example 20 (0.1-1 mg/kg) produced an augmentation of the ICP/BP responses elicited by sub-maximal stimulation of the cavernous nerve. A significant increase in the ICP/BP ratio was observed at doses from 0.1-1.0 mg/kg of compound tested." (Column 23, L. 48) **Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H600–H608, 1998.** The Ca^{2+}-sensitiveK^{+} channel (maxi-K^{+}) is an important modulator of corporal

	smooth muscle tone. The goal of these studies was twofold: 1) to determine the feasibility of transfecting corporal smooth muscle cells in vivo with the hSlo cDNA, which encodes for the human smooth muscle maxi-K^+ channel, and 2) to determine whether transfection of the maxi-K^+ channel would affect the physiological response to cavernous nerve stimulation in a rat model in vivo. Intracorporal microinjection of pCMVβ/Lac Z DNA in 10-wk-old rats resulted in significant incorporation and expression of β-galactosidase activity in 10 of 12 injected animals for up to 75 days postinjection. Moreover, electrical stimulation of the cavernous nerve revealed that, relative to the responses obtained in age-matched control animals (N=12), intracavernous injection of naked pcDNA/hSlo DNA was associated with a statistically significant elevation in the mean amplitude of the intracavernous pressure response at all levels of current stimulation (range 0.5-10 mA) at both 1 mo (N=5) and 2 mo (N=8) postinjection. Furthermore, qualitatively similar observations were made at 3 mo (N=2) and 4 mo (N=2) postinjection. These data indicate that naked hSlo DNA is quite easily incorporated into corporal smooth muscle and, furthermore, that expression is sustained for at least 2 mo in corporal smooth muscle cells in vivo. Finally, after expression, hSlo is capable of measurably altering nerve-stimulated penile erection. Taken together, these data provide compelling evidence for the potential utility of gene therapy in the treatment of erectile dysfunction. (p.H600, abstract (full))

The evidence within these references confirm that one of ordinary skill in the art would recognize not only that the claimed compounds possess BK channel opening activity, but would also correlate such activity with the treatment of the diseases recited in the claims.

In view of the above amendments, arguments and evidence, Applicants believe that the rejection under 35 USC 112, 1st paragraph should be withdrawn and that the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Gerald M. Murphy, Jr., Reg. No. 28,977 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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